



# Influence of Tobacco Smoking on Perioperative Risk of Venous Thromboembolism

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## Abstract

Venous thromboembolism (VTE) is generally considered a process very different from arterial atherosclerosis. The role of tobacco is well known in arterial thrombosis. However, its role in VTE is less obvious and remains controversial. In this mini review, we analysed the literature to identify the role of active or passive smoking in perioperative VTE and the relationship between arterial atherosclerosis and VTE. We carried an Internet search in French and English including the following keywords: deep vein thrombosis, tobacco, cigarette smoking, pulmonary embolism, postoperative, postoperative, atherosclerosis. Regarding the relationship between tobacco and VTE, a total of 9 studies were identified. Studies were ranked by the risk of VTE in relation to active or passive smoking. In conclusion, the management of smoking during the perioperative period for a short-term arrest (minimum 4–8 weeks before the intervention), or long term, allows among others a reduction of arterial or venous thrombotic events. However, it is clear that the training of anaesthesiologists in the management of smoking will contribute to the reduction of this public health problem.

**Keywords:** Atherosclerosis, cigarette smoking, deep vein thrombosis, pulmonary embolism, tobacco

## Introduction

Smoking is a major cardiovascular risk factor. More than 1% of cardiovascular deaths worldwide are attributed to smoking, which is the largest single cause of preventable death. Tobacco may cause harm without an intensity threshold or duration of consumption and even moderate to low consumption may cause serious damage (1).

Venous thromboembolism (VTE) is the third most common cardiovascular disease. It causes a number of potentially fatal complications. The prevalence of VTE increases significantly in the first 12 weeks following surgery, with a greater incidence in overweight and obese than in lean patients (2). It remains a major public health problem.

Venous thromboembolism is generally considered to be a very different process than atherosclerosis. The role of tobacco is well established in arterial thrombosis, but the evidence of its role on VTE as a distinct risk factor is less obvious and remains controversial. Some studies reported higher risk in current smokers than in individuals who have never smoked (2). Nevertheless, several studies reported smoking to be an independent risk factor; thus, others have failed to demonstrate a relationship between smoking and VTE (3). Furthermore, in 2003, an Italian team observed an association between VTE and markers of atherosclerosis, suggesting that both pathologies share common favourable circumstances (4). It is clear that some smoking-related diseases are directly related to tobacco and VTE, such as cancer or chronic cardiovascular disease (4).

Every year, approximately 11 million patients undergo a surgical procedure under anaesthesia in France, and nearly 3 million are smokers (5):

1. Increases the risk of general complications (triples the risk of infection, coronary events, immediate serious respiratory complications, leading to higher transfer of patients to intensive care units),
2. Increases the risk of surgical complications (two to four times more scar-related complications, risk of herniation after laparotomy, mediastinitis, digestive suture release, thrombosis of vascular prostheses, delayed bone healing),
3. Similarly, in children, there is a relationship between the intensity of passive smoking and the frequency of respiratory complications in Ear, Nose & Throat surgery (ENT).

These perioperative complications increase the overall duration of smokers' hospitalisation in more complicated surgery for an average of 2–3 days (5).

Methodology	Quality level
Randomised studies	High quality
Observational studies with one result or randomised studies with bias	Moderate quality
Observational studies or randomised studies with double bias	Low
Case reports and case series	Very low

Factors that Decrease the Quality of the Study
Poorly designed studies
Indirect results, doubtful evidence
Heterogeneous studies including lack of analysis of subgroups
Inaccuracy in results or confidence interval
An important probability of bias

Study	Tobacco smoking & primary risk of thromboembolism	Tobacco smoking & secondary risk of thromboembolism	No difference tobacco smoking versus placebo	Classification & type of study
Sweetland et al. (2)	Yes	0	0	High, prospective cohort
Cheng et al. (3)	Yes	Yes	0	High, meta-analysis
Prandoni et al. (4)	No	Yes	0	Moderate, observational consistent study
Parv et al. (13)	Yes	Yes	0	Moderate, observational study
Agno et al. (14)	No	Yes	0	High, meta-analysis
Wattanakit et al. (15)	No	Yes	0	High, prospective cohort study
Enga et al. (16)	No	No	Yes	High, prospective cohort study
Musallam et al. (17)	No	Yes	No	High, prospective cohort study
Dulicek et al. (18)	No	No	Yes	High, prospective cohort study

In this paper, we present an analysis of the role of tobacco in the occurrence of perioperative VTE as described in the literature.

### Methods

A Medline, Cochrane and Embase search, including the following keywords, was carried out: *deep vein thrombosis, tobacco, cigarette smoking, pulmonary embolism, postoperative, atherosclerosis*.

**Inclusion/Exclusion Criteria:** Due to a limited number of studies linking VTE to tobacco, we included randomised clinical trials, controlled clinical trials and case series with the link between tobacco and VTE and/or between tobacco, atherosclerosis and VTE. The exclusion criteria were studies conducted before 1980, inaccessible complete text, duplicate studies and studies published in languages other than French or English.

Each included study was ranked for evidence of the influence of tobacco on VTE and/or the relationship between atherosclerosis and VTE. The risk probability ranking included high, moderate, or low relationship. Tables 1 and 2 show this ranking according to the type of study and the factors that decrease the study quality.

### Results

Regarding the relationship between tobacco and VTE, a total of 9 studies were included. Table 3 ranks the studies by the risk of VTE in relation to active or passive smoking. The studies were ranked according to evidence to high, moderate, low and very low.

### Discussion

#### *Pathophysiological data*

Classical medical education often emphasises the difference between arterial thrombosis and venous thrombosis by classi-

fying them as two different pathophysiological entities, partly as a result of the obvious anatomical differences, as well as their distinct clinical presentation (6). This probably represents

**Table 4. Classical risk factors for cardiovascular disease**

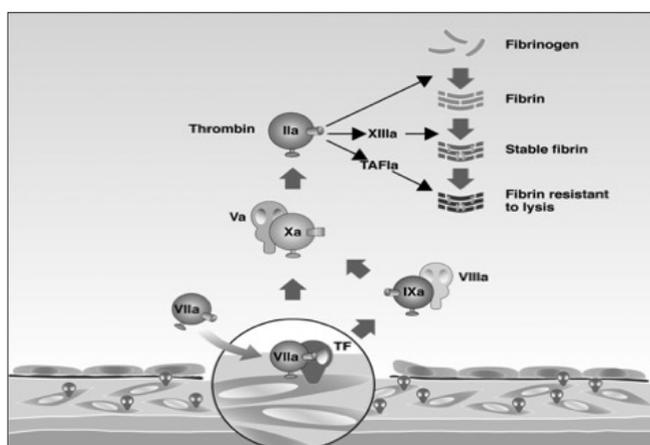
Risk factors	OR (99% CI)
Hyperlipidaemia	3.25 (2.81–3.76)
Smoking	2.87 (2.58–3.19)
Diabetes	2.37 (2.07–2.71)
Hypertension	1.91 (1.74–2.10)
Abdominal obesity	1.62 (1.45–1.80)

OR: Odds ratio; CI: confidence intervals. Reproduced with permission (10). Privetali et al. 'Risk factors for venous and arterial thrombosis.' *Blood Transf.* 2011; 9: 120-38.

**Table 5. Classical risk factors for venous thromboembolism**

High-risk factors (OR >10)	Moderate risk (OR 2–9)	Low-risk factors (OR<2)
Trauma or fractures	Non-oncological surgery	Age
Major orthopaedic surgery	Oral contraceptives and hormone replacement therapy	Bed rest >3 days
Oncological surgery	Pregnancy and puerperium	Prolonged travel
	Hypercoagulability	Metabolic syndrome
	Previous venous thromboembolism	Air pollution

OR, Odds ratio. Reproduced with permission (10) Privetali et al. 'Risk factors for venous and arterial thrombosis,' *Blood Transf.* 2011; 9: 120-38.



**Figure 1. Role of tissue factor and coagulation Factor VII in the activation of the coagulation cascade, leading to thrombin formation**  
 TAFI: Thrombin-activatable fibrinolysis inhibitor pathway inhibitor; 'a'=activated. Reproduced with permission (10) Privetali et al. 'Risk factors for venous and arterial thrombosis.' *Blood Transf.* 2011; 9: 120-38.

an oversimplification of the phenomenon (6). Although both types of thrombosis consist of platelets and fibrin (7), arterial thromboses tend to occur in the arterial plaque rupture, where the shear stresses are high; they are platelet-rich white thrombi, whereas venous thromboses occur where the venous wall is often normal, but the flow velocity and shear stresses are low (7).

The overall perioperative thromboembolic risk is the result of the patient-related risk factors and the specific risk of different types of surgery (8).

**Patient-related risk factors**

Patient-related risk factors grow linearly with age and become more important from the age of 40 and even more from the age of 60. Postoperatively, obesity by inducing a prolonged immobilisation and a decrease in fibrinolytic activity increases the risk of VTE (8). On the other hand, the major cancerous disease also increases the risk of VTE (8). Smoking is a direct (2, 3, 9) and indirect (6-8) risk factor. In a recent study, Delgado et al. (9) demonstrated that active smokers had higher values of fibrinogen, soluble fibrinogen and Factor XIII. Nevertheless, the same authors indicated that Factors VII, VIII, XII, the von Willebrand factor and the thrombomodulin (powerful inhibitor of coagulation) were also decreased. This indicates increased fibrin formation in active smokers (FA), a source of hypercoagulability (9), (Tables 4 and 5 present conventional risk factors for cardiovascular disease and VTE) (10).

Thrombophilia is considered to be predisposed to the formation of thrombosis. Atherosclerotic disease occurs after the erosion or rupture of atherosclerotic plaque, leading to the formation of platelet thrombosis in an arterial vessel with ischaemic manifestations (10). However, in VTE, the pathogenic mechanism remains partially known compared to that involved in atherosclerotic disease (10). It is currently accepted that stasis and hypercoagulability without endothelial injury are the cause of VTE (10). A venous thrombus is often formed of fibrin and red blood cells (4, 10). Normally, the coagulation process is controlled by several inhibitors. This delicate equilibrium may be interrupted by a coagulant action increased by coagulation factors and a reduced action of inhibitors resulting in the formation of thrombosis (Tables 4 and 5) (4, 10). In addition, in chronic smokers, a significant prolongation of activated thromboplastin and prothrombin times and a decrease in platelets were observed, factors favouring platelet aggregation (11). In short, tobacco increases the risk of VTE by multiple mechanisms by promoting an increased level of fibrinogen, coagulation Factors II, V, VIII, X and XIII, the tissue factor and homocysteine. The tissue factor and activated Factor VII play a crucial role in the activation of the coagulation cascade (10). Figure 1 shows the role of these two factors in the coagulation cascade.

The rate of these two factors increases with age, inflammatory conditions and smoking (10, 11). In addition, active smoking also promotes VTE by stimulating the activation and platelet aggregation and impairing fibrinolysis (11-13). However, tobacco is found as the sole risk factor in only 5% of patients. It is consistently found associated with one or more risk factors in the remaining patients (13).

Agno et al. (14) reported in their meta-analysis that obesity, diabetes, high blood pressure and dyslipidemia are also risk factors for VTE. However, Wattanakit et al. (15) in a study of more than 15,792 patients found that among risk factors for atherosclerosis and cardiovascular disease alone, obesity and smoking increased the risk of VTE.

### The specific risk of different types of surgery

The specific risk related to different types of surgery is divided into three categories, low, moderate and high (8).

The following classification for abdominal surgery can be used in other types of surgery. Accordingly, the risk of VTE in other surgeries (orthopaedic, gynaecological, urological, ENT, vascular, thoracic, cardiac etc.) is classified identically as low, moderate and high (8).

- 1) Low-risk: Non-major abdominal surgery-appendicitis, non-inflammatory gall bladder, proctology, parietal surgery,
- 2) Moderate risk: Extended and/or haemorrhagic dissection, abnormally prolonged operating time, emergencies,
- 3) High-Risk: Major abdominal surgery-liver, pancreas, colon, inflammatory or cancerous digestive tract disease, bariatric surgery.

Smoking is a public health problem that is particularly important during the perioperative period. In fact, a patient undergoing surgery is exposed to an increased risk of VTE (20, 21). A survey conducted in Great Britain between 2004 and 2005 reports that VTE is responsible each year for 25,000 deaths from pulmonary embolism (PE) (21). The thromboembolic risk in France is 183/100,000 inhabitants, including 123 venous thromboses and 60 pulmonary embolism cases (PE) (22). The risk of thromboembolism post-operatively is the result of two risks: the patient's own risk, of which smoking is a factor, and the specific risk induced by the type of surgery. The overall risk combines the two and can be also schematically divided into three levels: low, moderate and high (21). However, there is no specific study to quantify an overall level of risk (21). Nevertheless, the question remains whether the addition of several low and/or moderate risks significantly increases the level of risk (21). Active smoking before an intervention increases both the intra-hospital mortality and any complications that may occur (20). In France, approximately 11 million patients receive

anaesthesia each year, of which almost 30% are smokers (3 million patients) (20). Smoking increases all the specific surgical complications. The overall quality of the evidence is high for the analysis of all surgeries combined and very low to high for the analysis according to the type of surgery (20). VTE occupies an important place in the perioperative period. Situations that significantly increase the thrombotic risk, regardless of surgery, include a history of VTE, major familial thrombophilia, cancer, chemotherapy, heart failure or respiratory failure, hormone therapy, oestrogen-progestogen combined oral contraception, stroke with neurological deficit, postpartum, age, obesity, prolonged bed rest and smoking by direct or indirect action (20, 23).

In this work, a direct and indirect link between smoking and VTE has been demonstrated. Lowe (7) has demonstrated a strong link between arterial thromboses and venous thromboses. For example, under certain circumstances, arterial disease (MDI, stroke) may be directly provoked by the activation of haemostasis and indirectly by bed rest and association of blood stasis in the lower limbs that contribute to VTE (7). Other factors associated with smoking may increase the risk of postoperative VTE, such as age, obesity, smoking-related cancers, metabolic syndrome and diabetes (7). It appears that patients, with arterial thrombosis or venous thrombosis, share the same risk factors-hence the management that must cover the overall thrombotic risk. On the other hand, perioperative management of smokers who have had a prior arterial or venous thrombotic event must consider the added risk of smoking (7, 23).

Musallam et al. (17) in a large-scale multicentre study investigated the risk of vascular and respiratory events and the mortality rate in patients who smoked after the major surgery. The authors demonstrated that the postoperative mortality at 30 days following an arterial event (IDM, stroke), venous event (DVT, PE) and/or pulmonary infections, is significantly increased, independently of other associated cardiovascular events (17). Furthermore, Lind et al. (24) demonstrated that incident VTE was associated with an increased risk of cardiac and cerebral ischaemic manifestations.

It appears that active smoking slightly increases the risk of VTE in a direct way. It significantly increases this risk in combination with other risk factors, such as cancer, obesity, type of surgery, age and history of VTE (3). In addition, there is a reciprocal relationship between arterial and venous thromboses. Moreover, a causal relationship between smoking and VTE may be mediated by different mechanisms (3). Cheng et al. (3) suggest that the risk of VTE was not only solely due to smoking-related secondary diseases, but because they found a positive association between cur-

rent smoking and both provoked and unprovoked VTE (3). Furthermore, despite that epidemiological studies on the association of markers of atherosclerosis and VTE are divergent, data on the association of VTE with arterial thrombotic events (infarction and stroke) show an obvious relationship (7, 15).

## Conclusion

The management of smoking during the perioperative period for a short-term (minimum 4–8 weeks before surgery), or long term cessation (19), allows among other factors a reduction of arterial or venous thrombotic events. We suggest considering smoking as a high-risk factor for perioperative thrombotic events and to apply mechanical and pharmacological prophylaxis even in low-risk surgeries.

Despite the different recommendations of scientific societies and expert conferences, practices designed to help in preoperative smoking cessation are not uniform and sometimes not even proposed (25). The anaesthetist, the main actor of the perioperative period, must at least inform the patient of smoking risks. Questioning patients about their smoking status, advising them strongly to quit and connecting them to existing counselling resources are practical strategies to be incorporated in the perioperative setting. However, it is clear that the training of anaesthesiologists in the management of smoking addiction will contribute to the reduction of this source of public health problem.

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